SEQUENCE LISTING

The patent application contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (https://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20210395388A1). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

1.-79. (canceled)

80. An antigen-binding construct comprising a variant first antigen-binding polypeptide construct which monovalently binds a first HER2 ECD2 (human epidermal growth factor receptor 2 extracellular domain 2) antigen, the variant first antigen-binding polypeptide construct comprising

   a variable heavy (VH) domain comprising a complementary determining region (CDR) 1 (CDR-H1) comprising the sequence as set forth in SEQ ID NO: 956, a CDR-H2 comprising the sequence as set forth in SEQ ID NO: 957, and a CDR-H3 comprising the sequence as set forth in SEQ ID NO: 958; and

   a variable light (VL) domain comprising a CDR-L1 comprising the sequence as set forth in SEQ ID NO: 959, a CDR-L2 comprising the sequence as set forth in SEQ ID NO: 960, and a CDR-L3 comprising the sequence as set forth in SEQ ID NO: 609;

   and wherein the Glycine at position 56 of CDR-H2 has been substituted with a Tyrosine (H_G56Y) or a Phenylalanine (H_G56F), or the Serine at position 99 of CDR-H3 has been substituted with a Tryptophan (H_S99W), numbering according to Kabat numbering system;

   optionally wherein the variant first antigen-binding polypeptide construct comprises H_G56Y and further comprises the following substitution or set of substitutions, numbering according to Kabat numbering system:

H_K75W; or
H_T30Q; or
H_T30Y; or
H_S99W; or
L_Y49W; or
L_Y96G; or
H_S99W and L_Y49W; or
L_Y49W and L_Y96G; or
H_T30Q and L_Y49W; or
H_T30Q and H_S99W; or
H_T30Q and L_Y96G; or
H_T30Y and L_Y49W; or
H_T30Q and H_S99W and L_Y49W; or
H_T30Q and L_Y49W and L_Y96G; and

   optionally wherein the variant first antigen-binding polypeptide construct comprises H_S99W and further comprises the following substitution or set of substitutions, numbering according to Kabat numbering system:

H_K75W; or
H_T30Q; or
H_K75E; or
H_T30Y; or
H_K75W and L_Y49W; or
H_T30Q and H_K75W; or

H_T30Q and L_Y49W; or
H_T30Q and H_K75W and L_Y49W; or
H_K75W and L_Y49W and L_Y96G; or
H_T30Q and H_K75W and L_Y96G; or
H_T30Q and L_Y49W and L_Y96G; or
H_T30Q and H_G56Y and L_Y49W.

81. The antigen-binding construct of claim 80, wherein the VH domain comprises a sequence having at least 90% identity to the sequence set forth in SEQ ID NO:2 and the VL domain comprises a sequence having at least 90% identity to the sequence set forth in SEQ ID NO:11.

82. The antigen-binding construct of claim 80, wherein the Glycine at position 56 of CDR-H2 has been substituted with a Tyrosine (H_G56Y), numbering according to Kabat numbering system.

83. The antigen-binding construct of claim 82, wherein the variant first antigen-binding polypeptide construct further comprises the following substitution or set of substitutions, numbering according to Kabat numbering system:

H_K75W; or
H_T30Q; or
H_T30Y; or
H_S99W; or
L_Y49W; or
L_Y96G; or
H_S99W and L_Y49W; or
L_Y49W and L_Y96G; or
H_T30Q and L_Y49W; or
H_T30Q and H_S99W; or
H_T30Q and L_Y96G; or
H_T30Y and L_Y49W; or
H_T30Q and H_S99W and L_Y49W; or
H_T30Q and L_Y49W and L_Y96G.

84. The antigen-binding construct of claim 80, wherein the Serine at position 99 of CDR-H3 has been substituted with a Tryptophan (H_S99W), numbering according to Kabat numbering system.

85. The antigen-binding construct of claim 84, wherein the variant first antigen-binding polypeptide construct further comprises the following substitution or set of substitutions, numbering according to Kabat numbering system:

H_K75W; or
H_T30Q; or
H_K75E; or
H_T30Y; or
H_K75W and L_Y49W; or
H_T30Q and H_K75W; or
H_T30Q and L_Y49W; or
H_T30Q and H_K75W and L_Y49W; or
H_K75W and L_Y49W and L_Y96G; or
H_T30Q and H_K75W and L_Y96G; or